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(54) **CYCLOPENTA[D]PYRAZOLO[1,5-A]PYRIMIDINE COMPOUND AS CRF RECEPTOR ANTAGONIST**

CYCLOPENTA[D]PYRAZOLO[1,5-A]PYRIMIDIN-VERBINDUNG ALS CRF-REZEPTOR ANTAGONIST

COMPOSE CYCLOPENTA[D]PYRAZOLO[1,5-A]PYRIMIDINE COMME ANTAGONISTE DU RECEPTEUR DU CRF

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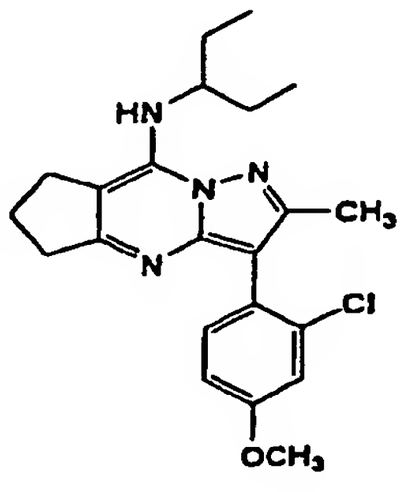
Description

[0001] The present invention relates to 8-(3-pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine of the following formula (I)



(I)

a pharmaceutically acceptable salt thereof or a hydrate thereof, which is useful as a pharmaceutical, and a pharmaceutical comprising them as an active ingredient.

Background

[0002] Corticotropin Releasing Factor (CRF) was a peptide comprising 41 amino acid residues and isolated from ovine hypothalamic in 1981. It was suggested that CRF was released from hypothalamic and controlled a secretion of adrenocorticotropic hormone (ACTH) from hypophysis [Science, 218, 377-379(1982)].

[0003] A biological effect is begun from CRF binds to CRF receptor, which exists on membranous surface of ACTH producing cell in anterior pituitary. Two subtypes of CRF receptors have been identified, and each one of these is distributed in a different area of brain. For example, a lot of receptor 1 is distributed in hypophysis, hypothalamic, cerebral cortex and a lot of receptor 2 is distributed in septal of brain, hypothalamus nucleus paraventricularis. Besides, receptors are also distributed in peripheral organ, for example, heart, gastrointestinal, lung, adrenal medulla, spleen, liver, renal, glandula prostatica. Concretely, receptor 1 is existed in bowel or spleen, receptor 2 is existed in stomach and especially receptor 2β is existed in heart and skeletal muscle.

[0004] ACTH, which is released by a stimulation of CRF, stimulates a secretion of cortisol from adrenal cortex, and relates to a systemic action for reproduction, growth, gastrointestinal function, inflammation, immune system, nervous system etc. Consequently, CRF is believed to plays a role as a regulator of these functions.

[0005] It was reported that excess CRF was secreted in brain of patient with depression and anxiety disorders [Science, 226, 1342-1343 (1984); Neuroscience and Behavioral Reviews, 22, 635-651 (1998); J. Endocrinol, 160, 1-12 (1999)].

[0006] Besides, a relation of CRF and various disorders was reported, for example, eating disorder [Science, 273, 1561-1564 (1996)], inflammation [Endocrinology, 137, 5747-5750 (1996)], irritable bowel syndrome [Am. J. Physiol, 253, G582-G686 (1987)], drug dependence [Psychopharmacology 137, 184-190 (1998)] and ischemia [Soc Neurosci Abstr (Nov 4.9, New Orleans), 807.6 (2000)].

[0007] On the other hand, CRF has an intimate involvement in stress. For example, administration of CRF to the brain elicited same behavior and endocrine response as an animal under stressful conditions [Nature, 297, 331 (1982)].

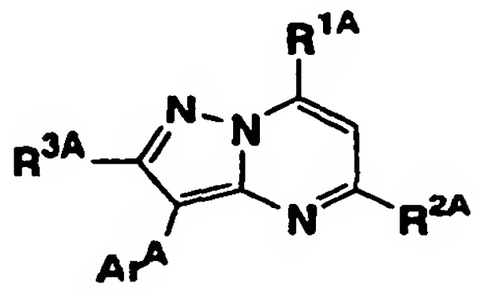
[0008] As above, a relationship of CRF and a disorder of central nerve system, neuropsychiatric disorder or a disorder of peripheral organ has been attracted attention.

[0009] Accordingly, an antagonism of CRF receptor is considered to be useful for a disease by abnormal secretion of CRF, for example, various diseases comprising stress-related disorders. For examples, it is believed to be useful for a prevention and / or treatment of depression, single episode depression, recurrent depression, postpartum depression, child abuse induced depression, anxiety, anxiety related disorders (e.g. panic disorder, particular phobia, fear of falling, social phobia, obsessive compulsive disorder), emotional disorder, bipolar disorder, posttraumatic stress disorder, peptic ulcer, diarrhea, constipation, irritable bowl syndrome, inflammatory bowel disease (ulcerative colitis, Crohn's disease), stress-induced gastrointestinal disturbance, nervous emesis, eating disorder (e.g. anorexia nervosa, bulimia nervosa), obesity, stress-induced sleep disorder, pain of muscular fiber induced sleep disorder, stress-induced immune suppression, stress-induced headache, stress-induced fever, stress-induced pain, post operative stress, rheumatoid arthritis, osteoarthritis, osteoporosis, psoriasis, thyroid dysfunction, uveitis, asthma, inappropriate anti- diarrhea hormone induced disorder, pain, inflammation, allergic disease, head injury, spinal cord injury, ischemic neuron injury, toxicity neuron injury, Cushing's disease, seizure, spasm, muscular spasm, epilepsy, ischemic disease, Parkinson's disease, Huntington

disease, urinary incontinence, Alzheimer's disease, senile dementia of Alzheimer type, multi-infarct dementia, amyotrophic lateral sclerosis, hypoglycemia, cardiovascular or heart-related disease (hypertension, tachycardia, congestive heart failure), drug addiction or alcohol dependence syndrome.

[0010] On the other hand, following compounds having an antagonism activity of CRF were known.

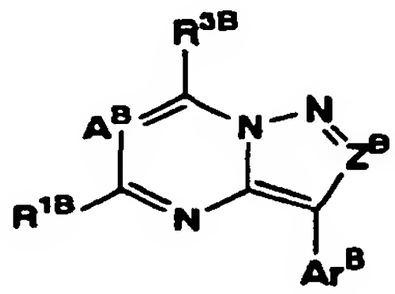
(1) In a specification of WO 97/29109, a compound of formula (A)



(A)

wherein R^{1A} is $NR^{4A}R^{5A}$ or OR^{5A};
R^{2A} is alkyl, alkyloxy, alkylthio;
R^{3A} is H, alkyl, alkylsulfonyl, alkylsufoxy or alkylthio;
R^{4A} is H, alkyl, mono- or di(cycloalkyl)methyl, cycloalkyl, alkenyl, hydroxyalkyl, alkylcarbonyloxyalkyl or alkyloxyalkyl;
R^{5A} is alkyl, mono- or di(cycloalkyl)methyl, Ar^{1A}-CH_2, alkenyl, alkyloxyalkyl, hydroxyalkyl, thienylmethyl, furanylmethyl, alkylthioalkyl, morpholinyl etc.;
or R^{4A} and R^{5A} taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl, optionally substituted with alkyl, alkyloxyalkyl;
Ar^A is phenyl, phenyl substituted with 1, 2 or 3 substitutes independently selected from halo, alkyl, trifluoromethyl, hydroxy, etc.; pyridinyl, pyridinyl substituted with 1, 2 or 3 substitutes independently selected from halo, alkyl, trifluoromethyl, hydroxy;
was described as CRF receptor antagonist.

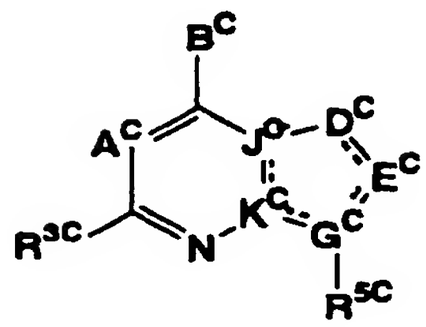
(2) In a specification of WO 98/03510, a compound of formula (B)



(B)

wherein A^B is N or CR^B;
Z^B is N or CR^{2B};
Ar^B is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, etc., each Ar^B optionally substituted with 1 to 5 R^{4B};
R^B is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, halo, cyano or haloalkyl;
R^{1B} is H, alkyl, alkenyl, alkynyl, halo, cyano or haloalkyl, hydroxyalkyl, etc.;
R^{2B} is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, etc.;
R^{3B} is H, OR^{7B}, SH, $S(O)_nR^{13B}$, COR^{7B}, CO_2R^{7B}, $OC(O)R^{13B}$, $NR^{8B}COR^{7B}$, $N(COR^{7B})_2$, $NR^{8B}CONR^{6B}R^{7B}$, $NR^{8B}CO_2R^{13B}$, $NR^{6B}R^{7B}$, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, etc.;
R^{4B} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, NO_2, halo, cyano, haloalkyl, $NR^{6B}R^{7B}$, $NR^{8B}COR^{7B}$, etc.;
was described as CRF receptor antagonist.

(3) In a specification of WO 98/08847, a compound of formula (C)

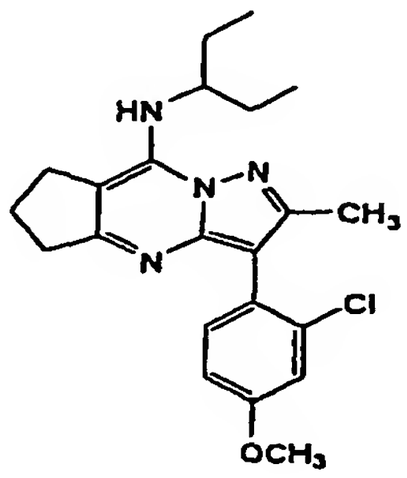


(C)

wherein the dashed lines is optional double bonds;
A^C is nitrogen or CR^{7C};
B^C is $NR^{1C}R^{2C}$, $CR^{1C}R^{2C}R^{10C}$, $C(=CR^{2C}R^{11C})R^{1C}$, $NHCR^{1C}R^{2C}R^{10C}$, $OCR^{1C}R^{2C}R^{10C}$, $SCR^{1C}R^{2C}R^{10C}$, $CR^{2C}R^{10C}NHR^{1C}$, $CR^{2C}R^{10C}OR^{1C}$, $CR^{2C}R^{10C}SR^{1C}$ or COR^{2C};
J^C and K^C are each independently nitrogen or carbon and both are not nitrogens;
D^C and E^C are each selected, independently, from nitrogen, CR^{4C}, C=O, C=S, sulfur, oxygen, $CR^{4C}R^{6C}$ and NR^{8C};
G^C is nitrogen or carbon;
The ring containing D^C, E^C, G^C, K^C and J^C may be a saturated or unsaturated 6-membered ring and optionally substituted with one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may optionally have one or two C=O or C=S; R^{1C} is alkyl optionally substituted with one or two substitutes independently selected from hydroxy, fluoro, chloro, bromo, iodo, O-alkyl, CF_3, C(=O)O-alkyl, OO(=O)alkyl, etc.;
R^{2C} is alkyl, which may optionally contain from one to three double or triple bonds, aryl or arylalkyl, cycloalkyl, cycloalkylalkyl, etc.;
R^{3C} is H, alkyl, O-alkyl, chloro, fluoro, bromo, iodo, alkylene-O-alkyl, alkylene-OH or S-alkyl;
R^{4C} is H, alkyl, fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, alkylene-OH, CF_3, etc;
R^{5C} is phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and each group is substituted with from one to four substitutes R^{13C}, wherein one to three of said substitutes may be selected, independently, from fluoro, chloro, alkyl and O-alkyl, and one of said substitutes may be selected from bromo, iodo, formyl, OH, alkylene-OH, alkylene-O-alkyl, cyano, CF_3, nitro, amino, alkylamino, dialkylamino, etc.;
was described as CRF receptor antagonist.

Disclosure of the Invention

[0011] The present invention relates to 8-(3-pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine of the following formula (I)



(I)

a pharmaceutically acceptable salt thereof or a hydrate thereof, and

(2) a pharmaceutical composition comprising them as CRF receptor antagonist.

[0012] Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkoxy, alkylene and alkynyl include straight and branched isomers. Isomers based on double bond, ring, fused ring (E, Z, cis, trans), isomers resulting from the presence of asymmetric carbon(s) (R-configuration, S-configuration, α-configuration, β-configuration, enantiomers, diastereoisomers), optically active compounds having optical rotation (D, L, d, l-configuration), polar compounds obtained by chromatographic separations (highly polar compound, less polar compound), equilibrium

compounds, the mixtures are existed by free ratio, racemic mixtures are included in the present invention.

[Salt]

[0013] The compound of the present invention of formula (I) may be converted into a corresponding pharmaceutically acceptable salt by known methods. In the present invention, pharmaceutical acceptable salts are salts of alkali metals, salts of alkaline-earth metals, ammonium salts, amine salts, acid addition salts.

[0014] Non-toxic and water-soluble salts are preferable. Appropriate salts are, salts of alkali metals, such as potassium, sodium; salts of alkaline-earth metals, such as calcium, magnesium; ammonium salts, pharmaceutically acceptable organic amines, such as tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylaminomethane; lysine, arginine, N-methyl-D-glucamine. A salt of alkali metal is preferable.

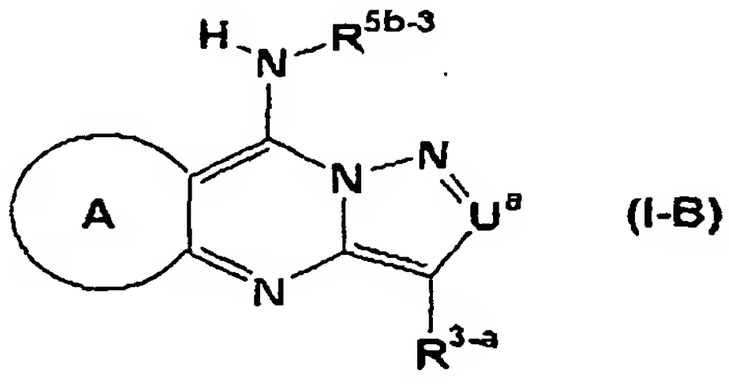
[0015] Non-toxic and water-soluble acid addition salts are preferable. Appropriate acid addition salts are, salts of inorganic acids, such as hydrochloride, hydrobromide, sulfate, phosphate, nitrate; salts of organic acid, such as acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethionate, glucuronate, gluconate.

[0016] The compound of formula (I) of the present invention and salts thereof may be converted into the corresponding hydrates by conventional means.

Preparation of the compound of the present invention

[0017] The present compound of formula (I) may be prepared, for example, by the following method.

[0018] The compound of formula (I-B)



(I-B)

wherein $R^{5b.3}$ is C1-15 alkyl;
U^a i s CR^2;
R^2 is

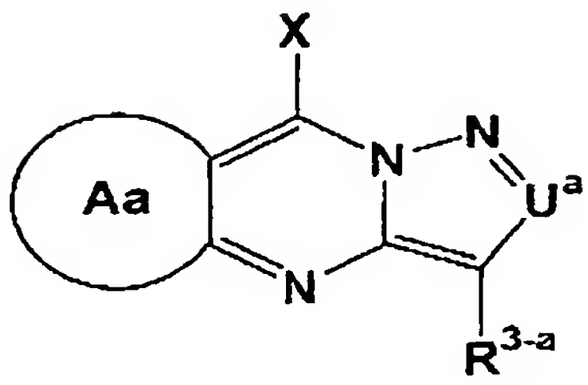
(i) hydrogen, or
(ii) C1-8 alkyl,

is C4-6 carbocyclic ring,

R^{3-a} is C5-10 mono- or bi-carbocyclic ring substituted by 1-5 of R^{16},
R^{16} is (a) OCH_3, or

(b) halogen atom;

may be prepared by reacting the compound of formula (IV)



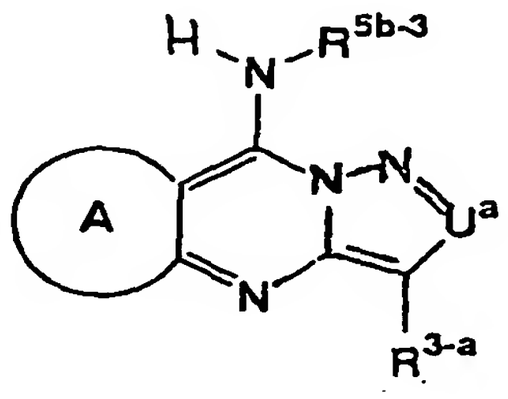
(IV)

wherein X is halogen atom, Aa ring is saturated or partially saturated C4-6 carbocyclic ring, the other symbols are as hereinbefore defined;
with the compound of formula (V-1)

$$H\text{-}N\text{-}R^{5b\text{-}3} \qquad (V\text{-}1)$$

wherein $R^{5b\text{-}3}$ is as hereinbefore defined.

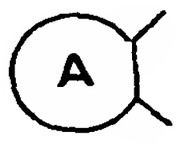
[0019] The compound (I-B-3)



(I-B-3)

wherein $R^{5b\text{-}3}$, is C1-15 alkyl;
U^a is CR^2;
R^2 is

(i) hydrogen, or
(ii) C1-8 alkyl,



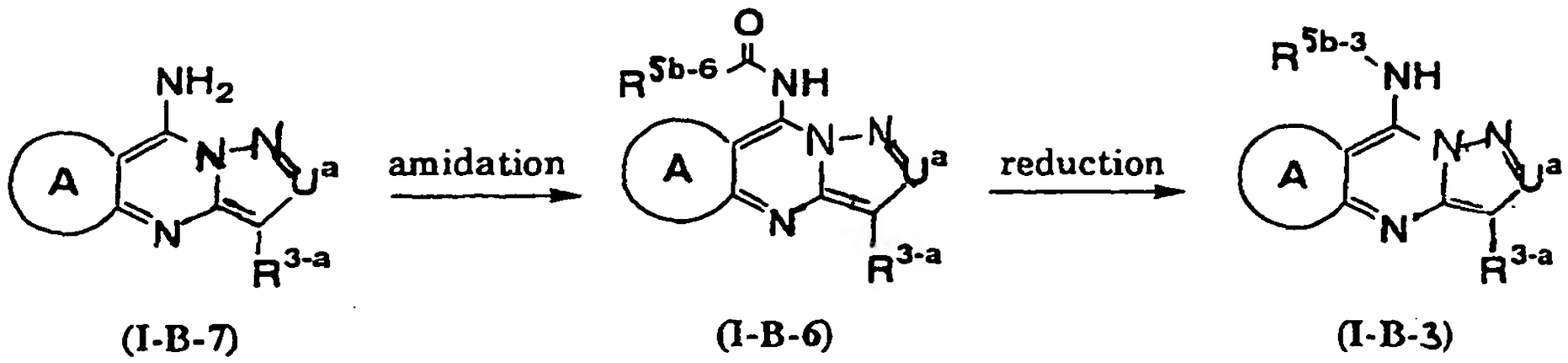
is C4-6 carbocyclic ring,

$R^{3\text{-}a}$ is $C_{5\text{-}10}$ mono- or bi-carbocyclic ring substituted by 1-5 of R^{16},
R^{16} is (a) OCH_3, or

(b) halogen atom;

may also be prepared according to the following Scheme (1).

Scheme (1)



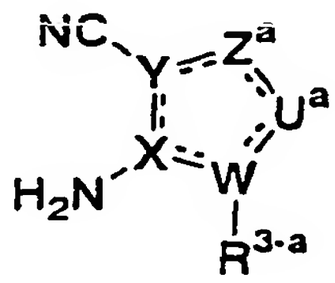
(I-B-7) (I-B-6) (I-B-3)

[0020] In Scheme (1), R^{5b-6} is C1-14 alkyl and the other symbols are as hereinbefore defined.

[0021] Amidation reaction is known, for example, it is carried out in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether, tetrahydrofuran) or without a solvent, using an acyl halide (e.g. oxalyl chloride or thionyl chloride etc.) at -20 °C ~ reflux temperature, and then the obtained acyl halide derivative may be reacted with amine, in an organic solvent (e.g. chloroform, methylene chloride, diethyl ether, tetrahydrofuran), in the presence of a tertiary amine (e.g. pyridine, triethyl amine, dimethyl aniline, dimethylaminopyridine) at 0-40 °C. The reaction may be carried out under an inert gas (e.g. argon, nitrogen) to avoid water in order to obtain a preferable result.

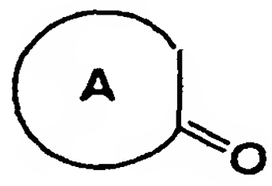
[0022] Reductive reaction is known, for example, it is carried out in an organic solvent (e.g. tetrahydrofuran), using a reducing agent (e.g. borane dimethylsulfide complex, lithium aluminum hydride) at 0 °C ~ reflux temperature.

[0023] The compound of formula (I-B-7) may be prepared by reacting the compound of formula (II-2)



(II-2)

wherein all symbols are as herein above defined;
with a compound of formula (III-2)



(III-2)

wherein all symbols are as herein above defined;
or successively, subjecting to oxidative reaction.

[0024] The above reaction of the compound of formula (II-2) and the compound of formula (III-2) is known, for example, it is carried out in an organic solvent (e.g. benzene, toluene) using an acid (e.g. p-toluenesulfonic acid or hydrate thereof) at from room temperature to reflux temperature, and successively, in an organic solvent (e.g. tetrahydrofuran), using base (e.g. lithium isopropylamide) at -10 ~ 50 °C.

[0025] And the starting materials and reagents in the present invention may be known per se or may be prepared by known methods.

[0026] In each reaction in the present specification, reaction products may be purified by conventional purification techniques, e.g. by distillation under atmospheric or reduced pressure, by high performance liquid chromatography, by thin layer chromatography or by column chromatography using silica gel or magnesium silicate; or by washing or by

recrystallization. Purification may be carried out after each reaction or after a series of reactions.

Brief Description of the Drawings

[0027]

Figure 1 shows a graph of the time spent in the open arms of rats that were administered 1, 3, 10 and 30 mg/kg of the present compound.
Figure 2 shows a graph of the number of entries into the open arms of rats that were administered 1, 3, 10 and 30 mg/kg of the present compound.

Pharmacological Activities

[0028] The compound of the present invention of formula (I) possesses CRF receptor antagonistic activity, for example, such an effect of the compound of the present invention was confirmed by following tests.

(1) Binding assay

[cell membrane preparation]

[0029] After the cell line expressing human CRF1 receptor (expressed cell line: CHO-K1 cells) was cultured to reached confluence, the cells were harvested with a scraper. Harvested cells were washed twice with PBS before being suspended in binding assay buffer (Tris-HCl (50 mM, pH 7.0), EDTA (2 mM, pH8.0), $MgCl_2$ (10 mM)) cooled by ice. Suspended cells were homogenized with a Downs-type homogenizer and subjected to centrifugation at 10,000g to collect the membrane fraction. The harvested cell membrane fraction was resuspended with a small quantity of the binding assay buffer, and further diluted with said buffer to 1 mg/mL. The membrane fraction thus obtained was used for binding assay.

[binding assay]

[0030] Fifty μL of [^{125}I] h/r CRF prepared to 0.5 nM with binding assay buffer was added to siliconized 1.5 mL tubes. 1 μL of compounds diluted in appropriate multiples, DMSO (for total binding use), or h/r CRF solution (100 μM, for the non-specific binding use), respectively, added to the tubes. Samples of 50 μL each of the membrane fraction preparation were added to the tubes to initiate the reaction (final concentration of [^{125}I] h/r CRF: 0.25 nM), then the mixtures were incubated for 2 hours at room temperature. After termination of the reaction, tubes were subjected to centrifugation at 15,000g to collect the membrane fraction. The supernatant was discarded, and the pellet was rinsed twice with cooled PBS (-) containing 0.01% Triton X-100. Radioactivity values of the respective tubes were measured with a γ-counter.
[0031] The specific binding was derived by subtracting the non-specific binding value from the each binding value.
[0032] The results indicated that these invented compounds exhibited potent affinity on CRF1 receptor (IC_{50}: < 1 μM).

(2) A measurement of an antianxiety activity using the elevated plus-maze

[0033] Two arms (open and closed) of equal width and length (50 cm × 10 cm), which crossed at a right angle to form a plus maze, were elevated to a height 50 cm above the ground level. The closed arm had a wall of 40 cm. Lighting on both ends of the open arm was maintained at constant illumination. Thirty minutes after administration of various doses of test-compounds (5 mL/kg), male SD rats were placed in the center of the plus maze. The time spent(s) in the open arms and the number of entries into the respective arms were measured within a 5 minutes period. The investigation personnel for measuring the indexes positioned at a fixed location during the course of the experiment.
[0034] The result was shown in figure 1 and 2. These figures indicated that the time spent in the open arms was extend significantly and the number of entries into the open arms was increased significantly by an administration of 3 and 10 mg/kg of the compound of Example 2(1) of the present invention, that is it was shown an antianxiety effect.

[Toxicity]

[0035] The toxicity of the compounds of the present invention is very low and therefore, it is confirmed that these compounds are safe for use as medicine.

Industrial Applicability

[Application to Pharmaceuticals]

[0036] The compounds of the present invention of the formula (I) are useful, in order to possess CRF receptor antagonistic activity, for the prevention and/or treatment of diseases induced by extraordinary secretion of CRF, for example, depression, single episode depression, recurrent depression, postpartum depression, child abuse induced depression, anxiety, anxiety related disorders (e.g. panic disorder, particular phobia, fear of falling, social phobia, obsessive compulsive disorder), emotional disorder, bipolar disorder, posttraumatic stress disorder, peptic ulcer, diarrhea, constipation, irritable bowl syndrome, inflammatory bowel disease (ulcerative colitis, Crohn's disease), stress-induced gastrointestinal disturbance, nervous emesis, eating disorder (e.g. anorexia nervosa, bulimia nervosa), obesity, stress-induced sleep disorder, pain of muscular fiber induced sleep disorder, stress-induced immune suppression, stress-induced headache, stress-induced fever, stress-induced pain, post operative stress, rheumatoid arthritis, osteoarthritis, osteoporosis, psoriasis, thyroid dysfunction, uveitis, asthma, inappropriate anti- diarrhea hormone induced disorder, pain, inflammation, allergic disease, head injury, spinal cord injury, ischemic neuron injury, toxicity neuron injury, Cushing's disease, seizure, spasm, muscular spasm, epilepsy, ischemic disease, Parkinson's disease, Huntington disease, urinary incontinence, Alzheimer's disease, senile dementia of Alzheimer type, multi-infarct dementia, amyotrophic lateral sclerosis, hypoglycemia, cardiovascular or heart-related disease (hypertension, tachycardia, congestive heart failure), drug addiction or alcohol dependence syndrome.

[0037] For the purpose described above, the compounds of formula (I) of the present invention, non-toxic salts thereof, an acid addition salts thereof or hydrates thereof may be normally administered systemically or topically, usually by oral or parenteral administration.

[0038] The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment, etc. In the human adult, the doses per person at a time are generally from 1 mg to 1000 mg, by oral administration, up to several times per day, and from 0.1 mg to 100 mg, by parenteral administration, preferably intravenous administration, up to several times per day, or continuous administration between 1 and 24 hours per day into vein.

[0039] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases wherein doses lower than or greater than the ranges specified above may be used.

[0040] The compounds of the present invention may be administered in the form of, for example, solid compositions, liquid compositions or other compositions for oral administration, injections, liniments or suppositories for parenteral administration.

[0041] Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders and granules. Capsules include hard capsules and soft capsules.

[0042] In such solid forms, one or more of the active compound(s) may be admixed with vehicles, such as lactose, mannitol, glucose, microcrystalline cellulose, starch; binders, such as hydroxypropyl cellulose, polyvinylpyrrolidone or magnesium metasilicate aluminate; disintegrants, such as cellulose calcium glycolate; lubricants, such as magnesium stearate; stabilizing agents, and solution adjuvants, such as glutamic acid or aspartic acid; and prepared according to methods well known in normal pharmaceutical practice. The solid forms may, if desired, be coated with coating agents, such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate; or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

[0043] Liquid forms for oral administration include pharmaceutically acceptable solutions, suspensions and emulsions, syrups and elixirs. In such forms, one or more of the active compound(s) may be dissolved, suspended or emulsified into diluent(s) commonly used in the art, such as purified water, ethanol or a mixture thereof. Besides such liquid forms may also comprise some additives, such as wetting agents, suspending agents, emulsifying agents, sweetening agents, flavoring agents, aroma, preservative or buffering agent.

[0044] Injections for parenteral administration include sterile aqueous, suspensions, emulsions and solid forms that are dissolved or suspended into solvent(s) for injection immediately before use. In injections, one or more of the active compound(s) may be dissolved, suspended or emulsified into solvent(s). The solvents may include distilled water for injection, physiological salt solution, vegetable oil, propylene glycol, polyethylene glycol, alcohol, e.g. ethanol, or a mixture thereof. Injections may comprise some additives, such as stabilizing agents, solution adjuvants, such as glutamic acid, aspartic acid or POLYSORBATE80 (registered trade mark); suspending agents, emulsifying agents, soothing agent, buffering agents, preservative. They may be sterilized at a final step, or may be prepared and compensated according to sterile methods. They may also be manufactured in the form of sterile solid forms, for example, freeze-dried products, which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before use.

[0045] Other forms for parenteral administration include liquids for external use, ointments and endermic liniments, inhalations, sprays, suppositories and pessaries for vaginal administration which comprise one or more of the active compound(s) and may be prepared by methods known per se. Sprays may comprise additional substances other than

diluents, such as stabilizing agents, such as sodium sulfate; isotonic buffers, such as sodium chloride, sodium citrate or citric acid. For preparation of such sprays, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 may be used.

Best mode for carrying out the invention

[0046] The following reference examples and examples illustrate, but do not limit the present invention.

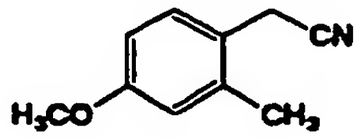
[0047] The solvents in parenthesis show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations and TLC.

[0048] The NMR data are shown with the solvent used in the measurements, in parentheses.

Reference Example 1

2-methyl-4-methoxyphenylacetonitrile

[0049]

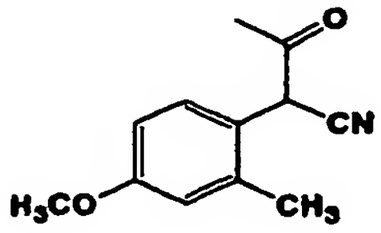


[0050] Under argon atmosphere, a mixture of N-bromosuccinimide (17.8 g) and 2, 2'-azobisisobutyronitrile (492 mg) was added to a solution of 1, 2-dimethyl-4-methoxybenzene (13.6 g) in carbon tetrachloride (200 ml). The mixture was refluxed for 6.5 hours. The reaction mixture was cooled with ice-bath. An insoluble matter was removed by filtration, and washed with carbon tetrachloride. A combined filtrate was concentrated. The residue was dissolved into N, N-dimethylformamide (100 ml) and sodium cyanide (9.86 g) was added to the mixture. The mixture was stirred over night at room temperature. The reaction mixture was poured into water, and the mixture was extracted with diethyl ether. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 6 → 1 : 4) to give the title compound (11.78 g) having the following physical data.
TLC: Rf 0.20 (n-hexane : ethyl acetate = 9 : 1);
NMR (300MHz, $CDCl_3$) : δ 7.24 (d, J = 8.0Hz, 1H), 6.78-6.72 (m, 2H), 3.79 (s, 3H), 3.60(s, 2H), 2.32 (s, 3H).

Reference example 2

1-cyano-1-(2-methyl-4-methoxyphenyl)propan-2-one

[0051]

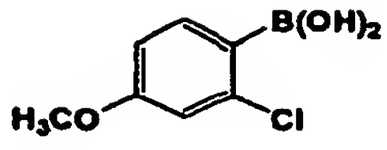


[0052] Under argon atmosphere, to a solution of the compound prepared in reference example 1 (11.7 g) in ethyl acetate (60 ml), metallic sodium (2.3 g) was added in numbers. The mixture was stirred for 2 hours at 50 °C. Ethyl acetate (40 ml) was added to the reaction mixture, and the mixture was refluxed for 2.5 hours and then it was stirred overnight at room temperature. A precipitation matter was collected by filtration, and it was washed with diethyl ether. The obtained crystal was dissolved into water (300 ml). The solution was adjusted pH 4 by adding 2N hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the title compound (12.06 g) having the following physical data.
TLC: Rf 0.45 (n-hexane : ethyl acetate = 1 : 1).

Reference example 3

2-chloro-4-methoxyboronic acid

[0053]

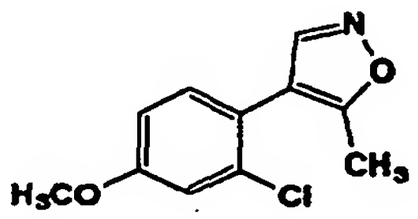


[0054] A solution of 3-chloro-4-bromoanisole (2.14 g) in anhydrous tetrahydrofuran (10 ml) was cooled at -78°C. 1.56 M n-butyl lithium / hexane (6.5 ml) was dropped into the solution, and the mixture was stirred for 30 minutes. Triisopropyl borate (2.3 ml) was dropped into the reaction mixture, and the mixture was stirred for 2 hours at -78°C. A saturated aqueous solution of ammonium chloride was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. A obtained solid was washed with t-butyl methyl ether (4 ml), filtered and dried over to give the title compound (681 mg) having the following physical data.
TLC: Rf 0.55 (methylene chloride : methanol =19 : 1) ;
NMR (300MHz, $CDCl_3$) : δ 7.22 (d, J = 8.4Hz, 1H), 6.93 (d, J = 2.4Hz, 1H), 6.86 (dd, J = 8.4, 2.4Hz, 1H), 3.79 (s, 3H).

Reference example 4

4-(2-chloro-4-methoxyphenyl)-6-methylisoxazole

[0055]

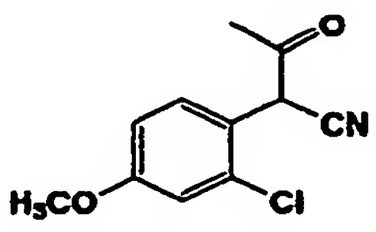


[0056] To a suspension of the compound prepared in reference example 3 (644 mg), 4-iodo-5-methylisoxazole (658 mg) and sodium bicarbonate (791 mg) in dimethoxyethane (2.6 ml) / water (2.5 ml), tetrakis (triphenylphosphine) palladium (36 mg) was added. The mixture was stirred for 16 hours at 80°C. To the reaction mixture that was cooled to room temperature, water and ethyl acetate were added. An insoluble matter was removed by filtration. An organic layer was separated from filtrate, it was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 19 : 1 → 15 : 1) to give the title compound (637 m g) having the following physical data.
TLC: Rf 0.44 (n-hexane : ethyl acetate = 3 : 1) ;
NMR (300MHz. $CDCl_3$): δ 8.29 (brs, 1H), 7.16 (d, J = 8.4Hz, 1H), 7.04 (d, J = 2.4Hz, 1H), 6.87 (dd, J = 8.4, 2.4Hz, 1H), 3.84 (s, 3H), 2.41 (brs, 3H).

Reference example 5

1-cyano-1-(2-chloro-4-methoxyphenyl)propan-2-one

[0057]

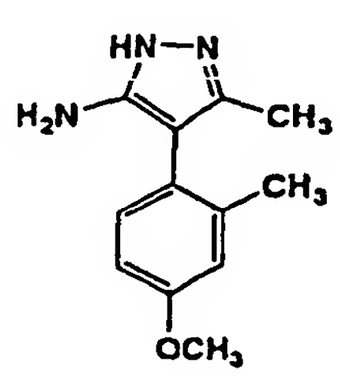


[0058] To a solution of the compound prepared in reference example 4 (623 mg) in methanol (2.8 ml), 1.5M sodium methoxide / methanol (2.8 ml) was added, and the mixture was stirred for 4 hours. The reaction mixture was diluted with water, and washed with hexane / t-butyl methyl ether (10 ml; 1:1). A water layer was adjusted pH 5 by adding 4N Hydrochloric acid (1 ml), and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated to give the title compound (497 mg) having the following physical data.
TLC: Rf 0.13 (n-hexane : ethyl acetate = 3 : 1) ;
NMR (300MHz, $CDCl_3$): 6 7.38 (d, J = 8.4Hz, 1H), 7.00 (d, J = 2.4Hz, 1H), 6.89 (dd, J = 8.4, 2.4Hz, 1H), 5.11 (s, 1H), 3.83 (s, 3H), 2.29 (s, 3H).

Reference example 6

5-amino-3-methyl-4-(2-methyl-4-methoxyphenyl)pyrazole

[0059]

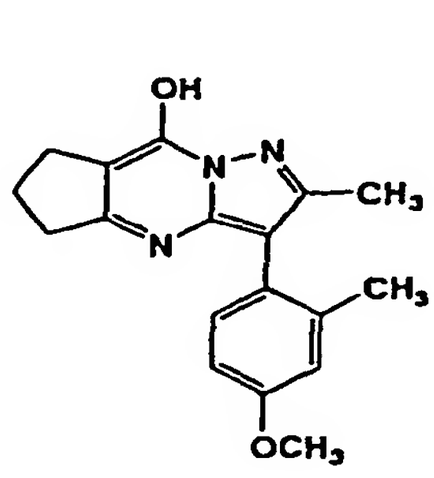


[0060] To a solution of the compound prepared in reference example 2 (8.63 g) in toluene (200 ml), acetic acid (8.0 ml) and hydrazine one hydrate (4.5 ml) were added. The mixture was refluxed for 5.5 hours and stirred overnight at room temperature. The reaction mixture was concentrated. 6N Hydrochloric acid was added to a residue, and the solution was extracted with ethyl acetate / n-hexane (30 ml / 30 ml). A water layer was basified by adding concentrated aqueous ammonia, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to give the title compound (8.38 g) having the following physical data.
TLC: Rf 0.30 (chloroform : methanol = 9 : 1) ;
NMR (300MHz, $CDCl_3$) : δ 7.08 (d, J = 8.0Hz. 1H), 6.84 (d, J = 2.5Hz, 1H), 6.77 (dd, J = 8.0, 2.5Hz, 1H), 4.10 (brs, 3H), 3.83 (s, 3H), 2.18 (s, 3H), 2.07 (s, 3H).

Example 1 (does not fall within the scope of the present invention)

8-hydroxy-2-methyl-3-(2-methyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine

[0061]



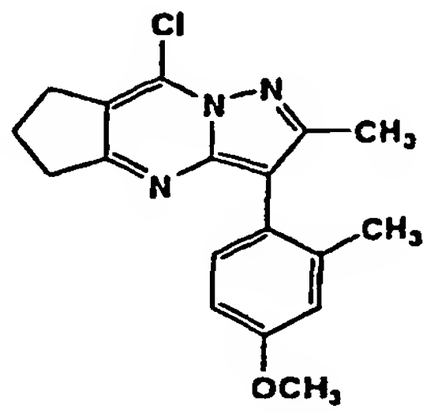
[0062] To a solution of the compound prepared in reference example 6 (500mg) in acetic acid (3 ml), ethyl cyclopentanone-2-carboxylate (0.40 ml) was added. And the mixture was refluxed for 3 hours. After the reaction mixture was cooled to room temperature, diethyl ether / n-hexane (10 ml; 2 : 1) was added to the mixture. A precipitated crystal was collected by filtration, and the crystal was washed with diethyl ether / n-hexane (10 ml; 2 : 1), dried over to give the title compound (480 mg) having the following physical data.
TLC: Rf 0.47 (chloroform : methanol = 9 : 1) ;

NMR (300MHz, DMSO-d_6) : δ 11.90 (brs, 1H), 7.10 (d, J = 8.0Hz, 1H), 6.93 (d, J = 3.0Hz, 1H), 6.83 (dd, J = 8.0. 3.0Hz, 1H), 3.78 (s, 3H), 2.81 (t, J = 7.5Hz. 2H), 2.66 (t, J = 7.5Hz, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (m, 2H).

Reference example 7

8-chloro-2-methyl-3-(2-methyl-4-methoxyphenyl)-6, 7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine

[0063]

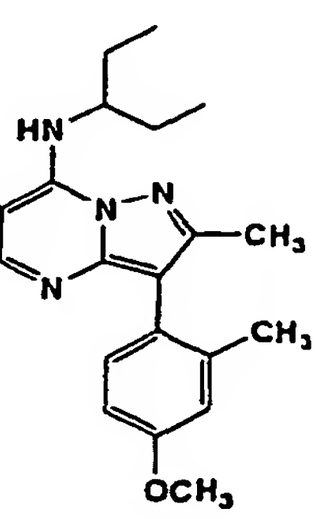


[0064] To a suspension of the compound prepared in Example 1 (400 mg) in toluene (4 ml), phosphorus oxychloride (0.60 ml) and diethylaniline (0.25 ml) were added. The mixture was refluxed for 1 hour. The reaction mixture was cooled, and it was poured into a cooled aqueous solution of sodium bicarbonate. The mixture was stirred for 10 minutes to degrade excess of phosphorus oxychloride. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 3 → 1: 2) to give the title compound (411 mg) having the following physical data.
TLC: Rf 0.52 (n·hexane : ethyl acetate = 1 : 1) ;
NMR (300MHz, $CDCl_3$): δ 7.15 (d, J = 8.5Hz, 1H), 6.88 (d, J = 2.5Hz, 1H), 6.81 (dd, J = 8.5, 2.5Hz, 1H), 3.83 (s, 3H), 3.09-3.00 (m, 4H), 2.40 (s, 3H), 2.23 (m, 2H), 2.15 (s, 3H).

Example 2 (does not fall within the scope of the present invention)

8-(3-pentylamino)-2-methyl-3-(2-methyl-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine

[0065]



[0066] A mixture of the compound prepared in reference example 7 (150 mg) and 3-pentylamine (0.6 ml) was stirred for 1 hour at 140 °C. The reaction mixture was cooled and purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1: 3) to give the title compound (169 mg) having the following physical data.
TLC: Rf 0.57 (n-hexane : ethyl acetate =1 : 1) ;
NMR (300MHz, $CDCl_3$): δ 7.15 (d, J = 8.5Hz, 1H), 6.85 (d, J = 3.0Hz, 1H), 6.78 (dd, J = 8.5, 3.0Hz, 1H), 6.21 (d, J = 10.5Hz, 1H), 3.82 (s, 3H), 3.81 (m, 1H), 3.08 (t, J = 7.0Hz, 2H), 2.89 (t, J = 8.0Hz, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 2.14 (m, 2H), 1.69 (m 4H), 1.02 (m, 6H).

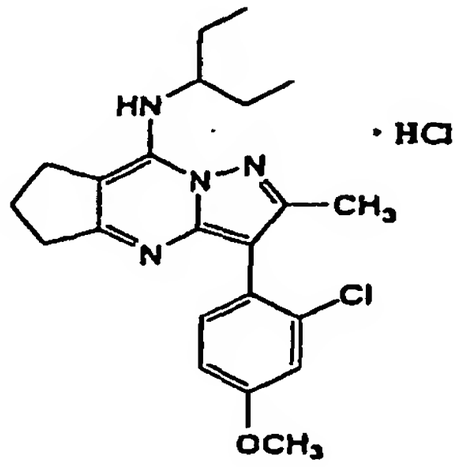
Example 2(1)

[0067] The following compound was obtained, using a corresponding compound in stead of 1,2-dimethyl-4-methoxybenzene, by the same procedure as a series of reactions of Reference example 1 → Reference example 2 → Reference example 6 → Example 1 using a corresponding compound in stead of ethyl cyclopentanone-2-carboxylate → Reference example 7 → Example 2 using a corresponding compound in stead of 3-pentylamine, or using the compound prepared in Reference example 5 or a corresponding compound, by the same procedure as a series of reactions of Reference example 6 → Example 1 → Reference example 7 → Example 2, or successively by a known method to be a salt of compound.

Example 2(1)

8-(3-pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6, 7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine hydrochloride

[0068]



TLC: Rf 0.20 (n-hexane : ethyl acetate = 3 : 1) ;
NMR (300MHz, pyridene-d_5 (0.5ml), $CDCl_3$ (0.1ml)) : δ 7.59 (d, J = 8.4Hz, 1H), 7.24 (d, J = 2.4Hz, 1H), 6.98 (dd, J = 8.4, 2.4Hz, 1H), 6.78 (d, J = 10.5Hz, 1H), 3.74 (m, 1H), 3.69 (s, 3H), 2.94 (t, J = 7.2Hz, 2H), 2.85 (t, J = 7.8Hz, 2H), 2.51 (s, 3H), 1.96 (m, 2 H), 1.64-1.48 (m, 4H), 0.91 (t, J = 7.5Hz, 6H).

Formulation examples (do not fall within the scope of the present invention)

Formulation example 1

[0069] The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

- 8-(3-pentylamino)-2-methyl-3-(2-methyl-4-methoxyphenyl)-6, 7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine 5.0 g
- Carboxymethylcellulose calcium (disintegrating agent) 0.2 g
- Magnesium stearate (lubricating agent) 0.1 g
- Microcrystalline cellulose 4.7 g

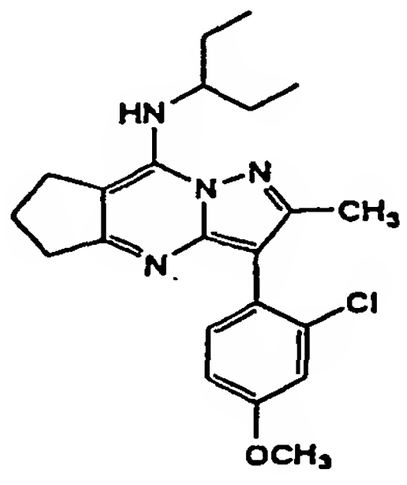
Formulation example 2

[0070] The following components were admixed in conventional method. The solution was sterilized in conventional manner, placed 5 ml portions into ampoules and freeze-dried to obtain 100 ampoules each containing 20 mg of the active ingredient.

- 8-(3-pentylamino)-2-methyl-3-(2-methyl-4-methoxyphenyl)-6, 7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine 2.0 g
- mannitol 20 g
- distilled water 500 ml

Claims

1. 8-(3-pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine of formula (I)



(I)

a pharmaceutically acceptable salt thereof or a hydrate thereof.

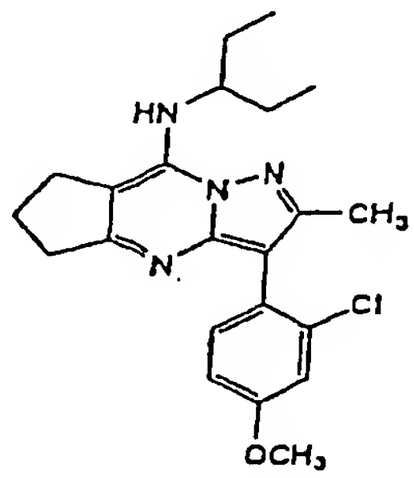
2. A pharmaceutical composition comprising a compound of the formula (I) as defined in claim 1.

3. Use of 8-(3-pentylamino)-2-methyl-3-(2-chloro-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine of formula (I) as defined in claim 1, a pharmaceutically acceptable salt thereof or a hydrate thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of diseases induced by extraordinary secretion of Corticotropin Releasing Factor.

4. Use according to claim 3, wherein the diseases induced by extraordinary secretion of Corticotropin Releasing Factor are selected from the group consisting of depression, single episode depression, recurrent depression, postpartum depression,

Patentansprüche

1. 8-(3-Pentylamino)-2-methyl-3-(2-chlor-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidin der Formel (I)



(I)

ein pharmazeutisch akzeptables Salz desselben oder ein Hydrat desselben.

2. Pharmazeutische Zusammensetzung, die eine Verbindung der Formel (I) gemäß der Definition in Anspruch 1 umfasst.

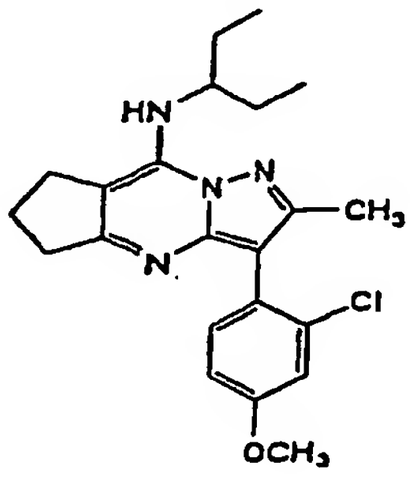
3. Verwendung von 8-(3-Pentylamino)-2-methyl-3-(2-chlor-4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo [1,5-a]pyrimidin der Formel (I) gemäß der Definition in Anspruch 1, einem pharmazeutisch akzeptablen Salz desselben oder einem Hydrat desselben zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung

und/oder Prävention von Erkrankungen, die durch eine außergewöhnliche Sekretion von Corticoliberin induziert werden.

4. Verwendung nach Anspruch 3, wobei die Erkrankungen, die durch eine außergewöhnliche Sekretion von Corticoliberin induziert werden, ausgewählt sind aus der Gruppe von Depression, Einzelepisodendepression, wiederkehrender Depression, Depression post partum, durch Kindesmissbrauch induzierter Depression, Angst, angstbedingten Störungen, Geistesstörung, manischdepressiver Psychose, posttraumatischer Belastungsstörung, peptischem Ulcus, Diarrhoe, Verstopfung, Reizdarmsyndrom, entzündlicher Darmerkrankung, belastungsinduzierter gastrointestinaler Störung, nervöser Emesis, Essstörung, Fettsucht, belastungsinduzierter Schlafstörung, durch Muskelfaserschmerzen induzierter Schlafstörung, belastungsinduzierter Immunsuppression, belastungsinduziertem Kopfschmerz, belastungsinduziertem Fieber, belastungsinduziertem Schmerz, postoperativem Stress, rheumatoider Arthritis, Osteoarthritis, Osteoporose, Psoriasis, Schilddrüsendysfunktion, Uveitis, Asthma, durch unpassendes Antidiarrhoehormon induzierter Störung, Schmerz, Entzündung, Allergieerkrankung, Kopfläsion, Rückenmarkläsion, ischämischer Neuronenläsion, Toxizitätsneuronenläsion, Cushing-Syndrom, Iktus, Spasmus, Muskelkrampf, Epilepsie, ischämischer Erkrankung, Parkinson-Krankheit, Chorea Huntington, Harninkontinenz, Alzheimer-Krankheit, Altersdemenz des Alzheimertyps, Mehrfachinfarktdemenz, amyotrophischer Lateralsklerose, Hypoglykämie, kardiovaskulärer oder herzbedingter Erkrankung, Drogensucht oder Alkoholabhängigkeitssyndrom.

Revendications

1. 8-(3-pentylamino)-2-méthyl-3-(2-chloro-4-méthoxyphényl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo[1,5-a]pyrimidine de formule (I)



(I),

sel pharmaceutiquement acceptable ou hydrate de ce composé.

2. Composition pharmaceutique comprenant un composé de formule (I) tel que défini dans la revendication 1.

3. Utilisation de la 8-(3-pentylamino)-2-méthyl-3-(2-chloro-4-méthoxyphényl)-6,7-dihydro-5H-cyclopenta[d]pyrazolo [1,5-a]pyrimidine de formule (I) telle que définie dans la revendication 1, d'un de ses sels pharmaceutiquement acceptables ou d'un de ses hydrates pour la préparation d'une composition pharmaceutique destinée au traitement et/ou à la prévention de maladies induites par une sécrétion extraordinaire du facteur de libération de la corticotropine.

4. Utilisation selon la revendication 3, dans laquelle les maladies induites par une sécrétion extraordinaire du facteur de libération de la corticotropine sont choisies dans le groupe constitué par la dépression, la dépression à épisode unique, la dépression récurrente, la dépression post-partum, la dépression induite par de mauvais traitements de l'enfant, l'anxiété, des troubles apparentés à l'anxiété, des troubles émotionnels, des troubles bipolaires, l'état de stress post-traumatique, l'ulcère peptique, la diarrhée, la constipation, le syndrome du côlon irritable, les maladies inflammatoires de l'intestin, les troubles gastro-intestinaux induits par le stress, les vomissements nerveux, les troubles de l'alimentation, l'obésité, les troubles du sommeil induits par le stress, les troubles du sommeil induits par une douleur des fibres musculaires, l'immunosuppression induite par le stress, les maux de tête induits par le stress, la fièvre induite par le stress, la douleur induite par le stress, le stress post-opératoire, la polyarthrite rhumatoïde, l'arthrose, l'ostéoporose, le psoriasis, les dysfonctionnements de la thyroïde, l'uvéite, l'asthme, les troubles induits par une hormone antidiarrhéique inappropriée, la douleur, l'inflammation, les maladies allergiques, le trau-

matisme crânien, les lésions de la moelle épinière, les lésions neuronales ischémiques, les lésions neuronales de toxicité, la maladie de Cushing, les attaques, les spasmes, les spasmes musculaires, l'épilepsie, les maladies ischémiques, la maladie de Parkinson, la maladie de Huntington, l'incontinence urinaire, la maladie d'Alzheimer, la démence sénile de type Alzheimer, la démence vasculaire, la sclérose latérale amyotrophique, l'hypoglycémie, les maladies cardio-vasculaires ou cardiaques, la toxicomanie ou le syndrome de dépendance à l'alcool.

REFERENCES CITED IN THE DESCRIPTION

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